Our Case No. 9793/116
Weickmann Ref. 11051P US-WO-1/WW
RDC Ref. RDID 0089 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Hans-Peter Josel et al.

Serial No. 08/776,190

Filing Date: January 24, 1997

For: Oligomeric Carrier Molecules with Defined Incorporated Marker Groups and Haptens

Examiner Mark Lance Shibuya

Group Art Unit No. 1639

DECLARATION UNDER 37 CFR § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Milan Mrksich, declare the following:

1. My curriculum vita is attached.

2. I am currently appointed as Professor of Chemistry at the University of Chicago. I received a B.S. degree in Chemistry from the University of Illinois and a Ph.D. degree in Chemistry from the California Institute of Technology. I served as an American Cancer Society Postdoctoral Fellow at Harvard University before joining the Chemistry Faculty at the University of Chicago in 1996.

3. I direct a research group of approximately twenty students and postdoctoral fellows. My program is in the field of Chemical Biology and is broadly directed towards the development of molecular reagents and surface chemistries for studies in biochemistry and cell biology. I have more than fifteen years of research experience, including expertise in the following areas: organic synthesis, molecular biology, surface chemistry, biosensors, and protein biochemistry.

4. I am the coauthor of more than 100 peer-reviewed research publications and am an Inventor on 6 patents. I serve or have served as a Consultant to several

biotechnology companies, including IGEN, Cellomics, Surface Logix, ChemoCentryx, Helicos and WMR Biomedical. I serve as Vice-Chair of the Defense Sciences Research Council which is an advisory group to the Defense Advanced Research Projects Agency. Further, I serve as Chair of the Enabling Biotechnology Review Group that evaluates proposals for the National Institutes of Health, and on the Board of Governors for Argonne National Laboratory.

5. United States patent application Serial No. 08/776,190 describes conjugates that are used in immunological assays. These assays take many forms, but in a common format the assay is used to analyze body fluids for antibodies that are produced in response to an infectious agent. Hence, the immunoassays are used, for example, to diagnose viral or bacterial infections in patients.

6. The claims relate to oligomeric molecules that are modified with haptens and either marker group(s) or immobilization group(s). The antigens are chosen so that they bind the antibody that is to be detected in a sample. The marker group(s) are chosen to permit observation of the oligomeric groups and the immobilization group(s) allow the oligomeric molecule to be attached to a solid phase. In one format, the antibody to be detected is incubated with an oligomeric reagent that both binds the antibody and carries a marker. This mixture is applied to a solid phase that also binds the antibody to be detected. If the antibody target is present in the sample, it will bind to the solid phase and serve to bind the oligomeric reagent to the solid phase, where it can then be detected by way of the marker.

7. Antigen reagents, such as those described above, have been prepared with a variety of methods. As the Applicants discuss, these reagents are often prepared by using synthetic polymers or biopolymers prepared with recombinant DNA methods. In both cases, the resulting reagents have limitations that can add to the cost and/or diminish the performance of the assay. Principal among these limitations is that it can be difficult to control the structures of the reagents. For example, the use of recombinant methods to prepare polypeptides is not effective for preparing many desired peptide sequences. In addition, the need to purify these reagents can lead to large variations in the properties of different batches.

8. The claimed invention recites a strategy that can prepare structurally well-defined oligomeric molecules, wherein the positions of the haptens, markers and immobilization groups can be defined precisely. In the language of the application, these sites are referred to as 'predetermined positions'. The method is based on using solid phase synthesis techniques to prepare linear oligomers—based on peptides, nucleic acids or peptide nucleic acids—that either incorporate the relevant groups at specified sites or that incorporate functional groups that permit a second reaction to introduce the groups at specified sites.

9. There are many benefits of using structurally well-defined and controlled oligomeric molecules. First, methods that give a single and well-defined molecule

are more reliable in reproducibly preparing the material of interest. Second, the ability to control the absolute and relative positions of the haptens or markers serves to optimize their functions. For example, if two fluorescent markers are positioned close to one another, the fluorescent signal may be quenched. Hence, the ability to optimize the relative positions of the markers is important to providing a maximum signal. Third, since each oligomeric molecule is identical, they will each have identical properties, avoiding the distribution in properties that are common with heterogeneous reagents.

10. The examiner has rejected claims 72-77, 81, 83-88, 100 and 107-115 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner maintains that the terminology "predetermined positions" 'does not convey structural limitations that would permit a person of skill in the art to determine what the invention is.' In stating this objection, the examiner apparently does not appreciate the scope of the invention, and the lack of necessity of detailing each possible configuration of a conjugate that would fall within the bounds of the invention. Indeed, the claimed invention can be applied to any number of specific purposes, and the structure of the conjugate will vary for each intended use. Again, it is not necessary for the Applicants to define the invention by listing all possible structures of conjugates that could be used. Rather, the functional definition provided throughout the application very clearly teaches one skilled in the art how to use the invention.

11. The Applicants unambiguously had possession of the "predetermined positions" element recited in the claims and, in my opinion, were in complete possession of conjugates wherein individual haptens, markers or immobilization groups are incorporated into the carrier at defined and reproducible "predetermined positions." In the introduction of the application, the Applicants have detailed many of the limitations that arise when using conjugates that have non-uniform presentations of haptens, markers and immobilization groups. It is imminently clear that the Applicants' invention addresses this limitation by providing conjugates that offer control over the relative and absolute positions of the haptens, markers and immobilization groups. As the Applicants stated (page 6), the invention "enables a defined and reproducible incorporation of hapten molecules and marker or solid phase binding groups into the conjugate. The distances between individual groups on the conjugate can be exactly defined and varied if necessary." The Applicants further stated (page 11-12) that the solid phase synthesis of the carrier allows that "monomer derivatives are introduced at predetermined positions on the carrier which are covalently coupled to hapten molecules or/and marker or solid phase binding groups or/and (b) after the synthesis activated hapten molecules or/and marker or solid phase binding groups are coupled to reactive side groups of the carrier." It is immediately apparent to one skilled in the art that the conjugates are not limited as to where the groups are attached to the carrier, but that the invention enables the preparation of a wide variety of conjugates.

12. The Applicants gave examples of the types of applications for which the conjugates are to be used, and provides a discussion that makes clear how the invention would be applied. For example, in cases where it is desired to incorporate multiple markers on a carrier so as to increase the strength of the observable signal in an assay, it is important to ensure that the markers do not interact with one another and diminish the observable signal. The Applicants recognized this important design parameter for conjugates on page 11, where it is stated that it is advantageous to use a carrier that "immobilizes the fluorescent marker groups with regard to spatial orientation and spacing in order to prevent fluorescence quenching by energy transfer. One skilled in the art recognizes that the specific parameters that determine the distances that should separate adjacent dyes will vary for different dyes, carriers, and assay conditions. Hence, it is not necessary, nor would it be efficient, to describe every possible conjugate that would fall within the scope of the invention for this particular use. Instead, the functional definition provided by the Applicants is unambiguously clear to one skilled in the art. Indeed, the skilled artisan would recognize that the invention offers control to install markers at specific predetermined positions, and these positions could be chosen so as to optimize the signal that can be detected from the markers.

13. The examiner has also rejected claims 72-77, 81, 83-88, 100 and 107-115 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for describing the structural limitations of a "non-immunologically reactive" carrier. Again, in stating this objection, the examiner apparently does not appreciate the scope of the invention, and the reason it is not necessary to describe each possible carrier structure that would render it "non-immunologically reactive".

14. The requirement that the carrier not react with antibodies in a test sample is certainly apparent to one having skill in the art. The purpose of the carrier is to present hapten molecules that bind to a specific antibody, and therefore to selectively identify the antibody from a complex mixture. Were the carrier itself, in the absence of the tethered hapten, to bind other antibodies in the sample, the assay would not be able to discriminate the specific antibody to be detected from the many other antibodies in the solution and therefore would give false information. Hence, it is readily apparent to those skilled in the art that the carrier must not interact with antibodies in the solution.

15. The Applicants were in possession of this element of the invention. The application unambiguously addressed this point on page 16, where Applicants stated "the peptide backbone of the conjugate has a non-immunologically reactive amino acid sequence i.e. an amino acid sequence which does not interfere with the test procedure in the intended application of the conjugate as an antigen in an immunological method of detection". Indeed, one skilled in the art will recognize that the Applicants' reference to an "intended application of the conjugate" is meant to address the invention to a large number of applications. The skilled

artisan will recognize that in each application, it will be important to use a carrier structure that does not interact with antibodies in a test sample—a so-called 'non-immunologically reactive' carrier—and that the specific structure of that carrier may vary with each application. Further, the skilled artisan will understand how to select or develop a carrier that meets this limitation.

16. The examiner has rejected claims 72-77, 81, 83-88, 100 and 107-115 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner stated that it "remains unclear as to whom the claimed positions are predetermined" and that the "claims or the specification do not reasonably apprise one skilled in the art as to the metes and bounds of the claimed invention." For the reasons discussed in paragraphs 10-12 of this declaration, the examiner's reasoning is flawed. It is indeed clear to one skilled in the art that the claimed conjugates will apply to a large number of applications, and that the specific structure of the conjugate—that is, the predetermined positions at which haptens, markers and solid phase binding groups are tethered—may vary for each intended application. Further, the skilled artisan will possess the skill to define the appropriate positions on the carrier for incorporation of the haptens, markers and solid phase binding groups. The Applicants' description of the invention in these functional terms is accurate, efficient and the most informative for those skilled in the art. Further, a skilled artisan would understand how they could avoid infringing these claims. For example, they could randomly introduce marker groups onto the polypeptide after the peptide synthesis is complete.

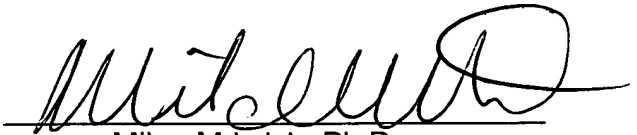
17. The examiner further states that it "remains unclear as to what identifies a carrier that is 'non-immunologically reactive'". The examiner states that the term is relative because "it is not clear what structural features produce a carrier that is 'non-immunologically reactive', regardless of the assay conditions." Here again, the examiner apparently seeks structural limitations that pertain to a non-immunologically reactive carrier. The examiner's assumption that there are structural features that produce a non-immunologically reactive carrier, regardless of the assay conditions, is flawed. Those skilled in the art recognize that the structural features that render a carrier non-immunologically reactive will depend on many parameters for the specific assay, including the source of the sample, the protocol for preparing the sample, the composition of the assay buffer, and other factors. Hence, it is not necessary to detail structural limitations for each and every possible application, for the reasons described in paragraphs 13-15 of this declaration. The skilled artisan recognizes these issues, and will recognize the limitations of the claims that pertain to non-immunologically reactive carriers and understand how to avoid them.

18. The examiner has rejected claims 72, 74, 75, 86-88, 100, 107, 110, and 111 under 35 U.S.C. 102 as being anticipated by Tam (U.S. Patent No. 5,229,490). The examiner submits that the Tam reference teaches a carrier that

simultaneously contains both a hapten molecule and a marker group. This analysis ignores a key distinction between the dendritic molecules described by Tam and the oligomeric molecules described by the Applicants. The Applicants require that the haptens, markers and immobilization groups are bound through an amino or thiol group. In the Tam reference, the solid phase is bound to the carrier through a hydroxyl group. The Applicants permit control in defining the absolute or relative positions of haptens, marker groups or immobilization groups. Dendrimers are highly symmetrical molecules and in practice it is exceedingly difficult—if not impossible—to introduce the haptens, marker groups or immobilization groups at predefined positions. In contrast, the oligomeric molecules described by the Applicants are prepared by solid phase synthetic methods that offer control over the positions of the haptens, markers groups and immobilization groups. Finally, the Tam reference does not address the limitations that derive from a non-optimal positioning of haptens, marker groups and immobilization groups on the dendritic particles. This reference does not describe any strategies that could be applied to optimize the positioning of these groups. Hence, the Tam reference does not anticipate the invention claimed by the Applicants.

19. The examiner has rejected claims 72, 74-76, 86-88, 100, 107, 110, and 111 under 35 U.S.C. 102 as being anticipated by Rose (U.S. Patent No. 6,001,364). The examiner submits that the Rose reference teaches that the attachment of a hapten or marker group or solid phase binding group may occur through a spacer. However, an important distinction between the method described in Rose and the method described by the Applicants is that the former teaches the preparation of a oligomeric molecule that is modified with only a single type of group, whereas the Applicants taught the preparation of an oligomeric molecule that contains the hapten at a set of predetermined positions and either a marker group or immobilization group at a set of predetermined positions. As the Examiner states in the office action, "the art teaches that it is an amino side group that has been reacted in order to attach the hapten or marker or solid phase binding group...(emphasis added)". Hence, in my opinion, the reference of Rose does not anticipate the invention claimed by the Applicants.

20. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: August 12, 2005 By: 

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